Biostatistical Review

PLA: *98-0207*
Roferon® A (Interferon alpha-2a) for the treatment of chronic hepatitis C.
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Roche Corporation

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BACKGROUND

Roferon® (Interferon alfa-2a) has been approved for the treatment of Hepatitis C (3 MIU tiw for 12 months).

The clinical study in this submission was designed as a multicenter, open-label, randomized Phase 3 trial to compare the safety and efficacy of two treatment periods (24-Week vs 48-Week) on the **ALT response at the end of 24 weeks of untreated follow-up**. Thus, the primary objective of this trial was to demonstrate the equivalence of 24 weeks of treatment to 48 weeks of treatment with respect to the sustained biochemical response (the primary endpoints). The overall design of the trial is shown in the attached diagram taken from the sponsor's submission.

A sample size of 197 patients per group was estimated on the assumption of a sustained ALT response rate of 30% in both groups, a delta value of 15%, a power of 90%, and an alpha level of 5%. The analytical plan specified that the equivalence between the two treatment arms would be accepted if the 95% confidence intervals were within the range of -15% to +15%.

Efficacy Results

I. The ALT Response in the Two Treatment Arms

Primary Efficacy The number and percentage of patients with a complete response (ALT and HCV RNA) at Week 48 and at Week 72 are summarized in Table 1.

The observed ALT response at the end of the 6-month untreated follow-up (the primary efficacy variable defined in the protocol) was 15.1% in the 24-Week treatment group and 18.6% in the 48-Week treatment group. The 95% confidence interval around this difference of 3.5% is –3.7% to +10.6%. Thus, it falls within the range of ± 15% specified in the protocol.

The two other important measures of efficacy - HCV RNA response and ALT + HCV RNA response – also give similar results (Table 1).

Table 1. ALT and HCV RNA response rates at the end of follow-up.

ENDPOINTS – TREATMENT ARMS	at Week 48 --- # of Pts (%)	at Week 72 --- # of Pts (%)	Percent Difference [95% CI]
ALT normal – 24 week (N=212)	32 (15.1)	22 (10.4)	
ALT normal – 48 week (N=210)	52 (24.8)	39 (18.6)	3.5 [-3.7, 10.6]
PCR negative – 24 week	27 (12.7)	20 (9.4)	
PCR negative – 48 week	44 (21.0)	30 (14.3)	1.6 [-5.0, 8.1]
ALT normal + PCR negative – 24 week	25 (11.8)	19 (9.0)	
ALT normal + PCR negative – 48 week	34 (16.2)	29 (13.8)	2.0 [-4.4, 8.4]

II. The ALT Response and Viral Genotypes

The results from earlier trials have shown that the patients with HCV genotypes 1a and 1b show lower response to IFN treatment as compared with 2b and 3a genotypes. The results on the sustained ALT response in various genotypes are given in Table 2. These data do confirm the general trend with respect to the lower ALT response in genotypes 1a and 1b. Also, there is a trend toward slightly higher response in 48-week arm in all genotypes.

Table 2. Sustained ALT Response by HCV Genotypes.

	IFN alfa-2a (6-3 MIU tiw) 24-Weeks N=212	IFN alfa-2a (6-3 MIU tiw) 48-Week N=210
HCV Genotype		
1a	10/89 (11.2%)	11/93 (11.8%)
1b	7/55 (12.7%)	10/55 (18.2%)
2b	5/28 (17.9%)	9/29 (31.0%)
3a	8/30 (26.7%)	7/22 (31.8%)
All others	2/10 (20.0%)	2/11 (18.2%)
TOTAL	**32/212 (15.1%)**	**39/210 (18.6%)**

COMMENTS

The results from this study show that the two treatment arms are equivalent (by the criterion defined in the protocol) with respect to the sustained ALT response (the primary efficacy variable). The sustained response rates, as defined by the HCV RNA measurements and the combination of ALT and HCV RNA rates, also show very similar results.